Appendix D: Summary of WATCHMAN Studies

Four additional clinical studies have been conducted on the WATCHMAN device as follows (in order of relevance):

Study	Enrollment Completion	Study Type and Objective
PILOT	January 26, 2005	Feasibility Study: first use of product; this study was not performed on the current design.
ASAP	November 22, 2011	Feasibility Study: related population contraindicated to warfarin therapy
WASP	Enrollment ongoing	Post-market registry in the Asia / Pacific region
EWOLUTION	Enrollment ongoing	Post-market region in Europe

Research Study of the WATCHMAN Left Atrial Appendage Filter System (PILOT)

Primary Objective: Evaluate the safety of the WATCHMAN device in subjects with non-valvular atrial fibrillation who required treatment for potential thrombus formation and were eligible for warfarin therapy.

Design: The study was a one-armed feasibility study intended to document Major Adverse Events (MAEs) specific to the study, which included ischemic stroke, systemic embolism, major bleeding and death as well as complications associated with the WATCHMAN device, both during the procedure and follow-up. Main entry criteria included, but were not limited to, age 18 or older, chronic or paroxysmal AF requiring treatment for potential thrombus formation and eligible for warfarin therapy. Pre-implant, subjects were evaluated with transesophageal echo (TEE) to rule out thrombus. After undergoing the implant procedure, patients were followed at 45 days, 6 months, 12 months, and annually thereafter. Repeat TEE were performed at 45 days and 6 months to verify device position and assess LAA closure.

Demographics: The average $CHADS_2$ in this population was 1.8±1.1. The average age was 69±8 years and the population was 34% female and 100% Caucasian.

Summary of Results: The WATCHMAN device was successfully implanted in 66/75 (88%) subjects, with discontinuation of warfarin in 68% at 45 days, 92% by six months, and 96% by 60 months. Mean follow-up in this study was 6.1 years. There were no deaths, no device embolizations related to the Gen 2.0/2.5 device, and no evidence of long-term erosion. These results supported progression to a pivotal study.

ASA Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology (ASAP Study)

Primary Objective: Characterize the performance of the WATCHMAN device in non-valvular atrial fibrillation (AF) subjects with contraindications to warfarin therapy. Subjects were prescribed aspirin and clopidogrel therapy post implant for 6 months rather than the usual six weeks of warfarin therapy.

Design: The study was a multicenter, prospective, non-randomized feasibility study of the WATCHMAN device in warfarin contraindicated subjects conducted at four investigational centers in Europe. In addition to a contraindication for warfarin, study participants were required to be at least 18 years of age and have recurrent non-valvular atrial fibrillation with a $CHADS_2$ score of 1 or greater, and an LVEF at least 30% or greater. Subjects were followed at 3, 6, 12, 18, and 24 months with TEE examinations at 3 and 12 months to assess the WATCHMAN device. This study did not have formal hypothesis testing but instead used descriptive statistics to characterize event rates for all-cause mortality, ischemic and hemorrhagic stroke, and device thrombus as well as serious procedure or device-related adverse events.

Demographics: The average $CHADS_2$ in this population was 2.8±1.2. The average age was 73±7 years and the population was 36% female. The most common contraindication to warfarin therapy was a history of bleeding tendencies (67%).

Summary of Results: The WATCHMAN device was successfully implanted in 142/150 (95%) subjects with a mean follow-up duration of 17 months. The deaths were adjudicated by an external Clinical Events Committee (CEC) and considered to not be device related. Detailed information is located in the ASAP Clinical Study Report. There was no evidence of long-term erosion. Event rates observed in the study are summarized in **Table 1**.

Table 1: ASAP Event rates

Event	Events/Pt-yrs (Rate per 100 Pt-yrs)
Death (All-Cause)	11/213.7 (5.1)
Stroke	5/209.0 (2.4)
Stroke - Ischemic	4/210.4 (1.9)
Stroke - Hemorrhagic	1/212.3 (0.5)
Device Thrombus	8/205.4 (3.9)

Ischemic stroke was reported in four (4) subjects for a rate of 1.9 per 100 pt-yrs. This rate is significantly lower than other trials assessing stroke rates in subjects with atrial fibrillation who are unable to take anticoagulant therapy. All stroke and ischemic stroke rates in ASAP were similar to those observed in the randomized non-inferiority PROTECT AF study despite having a higher $CHADS_2$ stroke risk. These results suggest that it may be safe to implant the WATCHMAN device in patients with contraindications to warfarin therapy.

Registry on WATCHMAN Outcomes in Real-life Utilization (EWOLUTION)

Primary Objective: Compile real-world clinical outcomes data for WATCHMAN LAA (Left Atrial Appendage) Closure Technology in patients who are implanted with the WATCHMAN device in a commercial clinical setting and collect real-world usage data that may be needed for reimbursement of WATCHMAN technology in certain countries.

Design: This is an observational, prospective, non-randomized, multicenter study. Approximately 1000 subjects will be enrolled in the study. To reduce the impact of individual center bias, each site may include up to 45 subjects and each country may include a maximum of 500 patients. Up to 70 sites in the International (Outside of US) region will be included in this study. Study participants are required to be eligible for a WATCHMAN device according to current international and local guidelines (and future revisions) and per physician discretion; willing and capable of providing informed consent, participating in all testing associated with this clinical investigation at an approved clinical investigational center; and at least 18 years of age, or of legal age to give informed consent specific to state and national law.

Primary analyses may include, but will not be limited to, the following: procedural complications and the incidence of stroke and death. Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study.

Each patient will be followed for a period of two years after enrolment according to the schedule and standard practice at the enrolling centers. There will be no additional visits, nor procedures, for subjects who participate in the study. Subjects are expected to be followed at implant, then at one post-implant visit (typically between 1-3 months of implant), and then annually through 2 years post implant. An intermediate visit may be a scheduled in a number of patients, per physician discretion. In order to reliably capture patient status at study end a FU window of 24 ± 3 months will be considered acceptable for scheduling the last visit.

Enrollment started in October 2013, and enrollment is ongoing. Subjects will be followed through their 2 year follow-up visit. At the time of this briefing document, 36 sites have opened and 327 patients have been enrolled.

WATCHMAN Asia Pacific Registry (WASP)

Primary Objective: Compile real-world clinical outcomes data for WATCHMAN LAA (Left Atrial Appendage) Closure Technology in patients who are implanted with the WATCHMAN device in a commercial clinical setting and to collect health care usage data that may be needed for reimbursement of WATCHMAN technology in certain countries.

Design: The study is an observational, prospective, non-randomized, multicenter study. Approximately 300 subjects will be enrolled in the study. To reduce the impact of individual center bias, each site may include up to 45 subjects and each country may include a maximum of 150 patients. Up to 10 sites in Asia region will be included in this study. Study participants are required to be eligible for a WATCHMAN device according to current international and local guidelines (and future revisions) and per physician discretion; willing and capable of providing informed consent, participating in all testing associated with this clinical investigation at an approved clinical investigational center; and at least 18 years of age, or of legal age to give informed consent specific to state and national law.

Primary analyses may include, but will not be limited to, the following: procedural complications, incidence of stroke and death. Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study. Enrolment is expected to be completed in 21 months; therefore the total study duration is estimated to be 48 months.

Each patient will be followed for a period of two years after implant according to the schedule and standard practice at the enrolling centers. There will be no additional visits, nor procedures, for subjects who participate in the study. Subjects are expected to be followed at implant, then at one post-implant visit (typically between 1-3 months of implant), and then annually through 2 years post implant. An intermediate visit may be scheduled in a number of patients, per physician discretion. In order to reliably capture patient status at study end a follow-up window of 24 ± 3 months will be considered acceptable for scheduling the last visit.

Enrollment started in January 2014, and enrollment is ongoing. Subjects will be followed through their 2 year follow-up visit. At the time of this briefing document, 7 sites have opened and 74 patients have been enrolled.